Letters to the Editors

Double injection *vs* skin microdialysis technique in minimally invasive *in vivo* pharmacology

Wenzel and colleagues recently concluded that an endothelin-A (ET-A) receptor antagonist attenuates the skin vasoconstriction produced by angiotensin II (Ang II) and noradrenaline (NA) [1]. The postulate that the selective ET-A antagonist, BQ123, blocks Ang II and NA mediated vasoconstriction challenges well-established physiological and pharmacological concepts, in particular, the notion of specific receptors for these peptidergic and nonpeptidergic substances. We believe that the double injection technique (DIT) used to assess blood flow of the skin microcirculation in this study has some drawbacks that might have affected the data generated from it.

In this study [1], skin blood flow was assessed immediately after injection of the study substance, which can give rise to confounding results as injection trauma can produce significant vasodilation [2]. Studies using microdialysis probes to visualize the changes in skin blood flow by laser-Doppler perfusion imaging demonstrate that a blood flow equilibrium period of about 60 min is required for the effects of trauma to dissipate [2]. The vasodilatory effects of local histamine released from injection trauma can last up to 40 min [2]. Hence, the effects of injection trauma cannot be distinguished from the effects of the study drug. It can be assumed that, in this study, the dilator effects of the control drug (i.e. saline or the antagonist) were subtracted from the vasodilation or vasoconstriction induced by the study drug. Regardless, subtracting the value does not ensure that the effects of histamine or other vasodilatory substances released by injection trauma will not be present during the study period of 30 min For example, BQ123 could have induced a nonspecific vasodilatory effect unrelated to blockade of ET-A receptors. Similarly, trauma could have affected the vasoconstrictor effects of Ang II and NA by release of local vasodilatory substances.

The combination of microdialysis and laser-Doppler flowmetry (Figure 1), with an equilibrium period of 2 h after insertion of the microdialysis probes, allows similar studies without the confounding effects of trauma. This technique allows for the study of vasodilatory and vasoconstrictor substances on skin blood flow even at the already low baseline flows found during normothermia and after resolution of trauma [3]. Using this technique, we have shown that the ET-B receptor antagonist (BQ788) at a dose of 1.5×10^{-7} mol l^{-1} produced cutaneous vasodilation in healthy men and vasoconstriction in healthy females. Therefore, we concluded that the contribution of ET-B receptors to resting vascular tone differs between males and females in the human cutaneous vasculature [4]. In contrast, the authors' in the present study [1] demonstrated a mild vasoconstriction with BQ788 in men at doses ranging from 10^{-8}-10^{-10} mol l^{-1}. This could result from an effect of BQ788 on the vasodilatory response produced by histamine or other local vasodilators, like nitric oxide, in response to trauma.

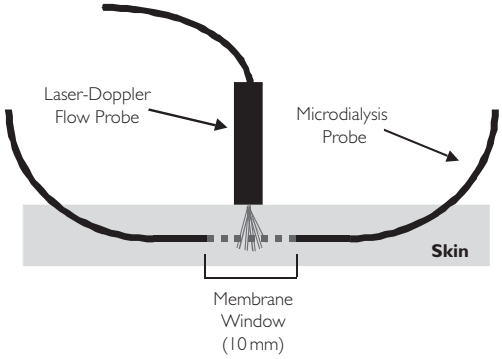

Figure 1 Diagram of the setup for measurement of skin blood flow in combination with microdialysis. The laser-Doppler probe is taped on the skin directly above the microdialysis fiber. The endsof the microdialysis fiber are exteriorized and connected to a microinfusion pump and a collection reservoir.

We agree with the comments of the senior author, in a recent review [5], regarding the need for a minimally invasive tool to assess human *in vivo* pharmacology especially, because other techniques are either more invasive (forearm blood flow studies using venous occlusion plethysmography and intra-arterial injections) or are unpredictable due to variable drug penetration (iontophoresis). Interpretation of data generated using DIT can be difficult due to the confounding effects of vasoactive and inflammatory substances released locally in response to trauma. Since the use of skin microcirculation as a surrogate for other areas of circulation is relatively new, it is imperative that investigators interested in this area agree on using techniques that minimize such confounding effects.

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Cyclosporin enhances the tendency towards oedema and flushing noted on dihydropyridine calcium channel blockers

Currently available calcium channels blockers are divided into two categories based upon their effect: the dihydropyridines, which cause arterial vasodilation but do not influence heart contractility and conduction, and the nondihydropyridines, which do not cause vasodilation but have negative effect upon heart conduction and contractility [1, 2]. The most commonly reported adverse events noted with dihydropyridines are peripheral oedema and flushing that occur in 10–20% of the patients, both children and adults. These adverse events do not occur with nondihydropyridines. The tendency to oedema is directly linked to the extent of arterial vasodilation that redistributes fluid from the vascular space into the interstitium and is not dependent on the type of the dihydropyridine [3, 4].

The nephrotoxicity of cyclosporin may be in part counterbalanced by calcium channel blockers [5]. On the other side, treatment with certain calcium channel blockers increases cyclosporin blood levels. The effect of the dihydropyridine amlodipine on cyclosporin metabolism is not as great as that seen with other calcium channel blockers. Consequently amlodipine is frequently prescribed in hypertensive patients on cyclosporin [6, 7].

Between 1994 and 2001 we treated at least 54 hypertensive patients (31 male and 23 female subjects, aged between 1.1 and 20, median 13 years) with amlodipine. Ten of the patients were on treatment with cyclosporin. Nine patients (four boys and five girls, aged 3.2–19, median 11 years) withdrew from amlodipine because of oedema, flushing or headache. They were 4 of the 10 patients (40%) with and 5 of the 44 patients (11%) without cyclosporin ($P < 0.02$, χ^2-test). The dosage of amlodipine was similar in the patients who developed oedema (from 0.10 to 0.36, median 0.26 mg kg^{-1} body weight once a day) and in those who failed to develop this complication (from 0.11 to 0.34, median 0.22 mg kg^{-1} body weight).

It has been stated that oedema and flushing are less common when calcium channel blockers are given with a converting enzyme inhibitor [3]. Thirteen of our 54 patients given amlodipine were on treatment with a converting enzyme inhibitor (enalapril, $n = 6$; ramipril, $n = 3$; captopril, $n = 3$; perindopril, $n = 1$). In our experience the tendency to develop oedema was not different in patients with (2 out of 13 patients; namely 15%) and in patients without (7 out of 41 patients; namely 17%) converting enzyme inhibitors.

The potential of calcium channel blockers to aggravate the gum enlargement caused by cyclosporin is well recognized [8]. The present data suggest the existence of a further unpleasant interaction between calcium channel blockers and cyclosporin: oedema and flushing are more common when the dihydropyridine amlodipine is given with cyclosporin. On the other hand, our experience with a limited number of patients does not corroborate data from the literature suggesting that oedema and flushing are less common when a dihydropyridine is given with a converting enzyme inhibitor [4].

In conclusion, peripheral oedema and flushing, the most commonly adverse events noted on treatment with dihydropyridine calcium channel blockers, occur more frequently in patients concomitantly treated with

cyclosporin and amlodipine. Our data do not provide any explanation for this association.

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Spontaneous reporting of adverse drug reactions in Cuba: integrating continuous education, training and research in a network approach

Spontaneous reporting of suspected adverse drug reactions (ADRs) is the most extended drug safety monitoring method. Currently, 65 countries participate in the WHO Programme for International Drug Monitoring.

Spontaneous reporting partly depends upon prescribers' knowledge, skills and willingness to report [1]. This can be favoured by means of close collaboration, regular contact, and provision of feedback information. The Cuban National Network of Pharmacoepidemiology (NNP) was set up in 1996. It consists in 175 centres, each one located at the chief pharmacy in every municipality of the country (with more than one centre in large cities). Each centre is run by an experienced family practitioner with additional training in pharmacoepidemiology. This was provided through a specific Diploma in Pharmacoepidemiology, with a 360 teaching hours programme in clinical pharmacology, methods in epidemiology, clinical trials, drug utilization studies, observational analytical studies, and other relevant methods for benefit/risk assessment. The whole NNP is coordinated by the Centre for the Development of Pharmacoepidemiology (CDP). The main objectives of the NNP are (a) disseminating accurate problem-orientated therapeutic information among health professionals, (b) implementing continuing education activities on drug therapy, with particular emphasis on common health problems and other therapeutic priorities identified through drug utilization studies, (c) carrying out research on drug utilization, and (d) promoting educational and administrative interventions aimed at improving drug prescription and use [2].

In 1994 Cuba became a member of the WHO Programme for International Drug Monitoring. In 1998, the Cuban System of Pharmacovigilance gathered around 900 reports (equivalent to a reporting rate of 75 per million inhabitants). In 1999 the responsibility for drug safety monitoring was transferred to the CDP, and a National Coordinating Unit of Pharmacovigilance was set up. Since then, promotion of ADR reporting became a part of the continuous education activities of the NNP. A plausible effect has been a dramatic increase in the yearly number of reports: in 1999, 21 125 reports were received (1920 per million inhabitants), and in 2000 the figure was 28 450 (2543 per million inhabitants). These rates are an order of magnitude higher than those achieved in those more developed countries with the highest reporting rates [3]. Table 1 shows additional information on the reports gathered in 2000.

The main limitations of spontaneous reporting are underreporting, selective reporting, and incomplete drug histories [4]. Different approaches have been tried in order to limit underreporting, such as adding a yellow card in the prescription pads of the national health system, inviting other health professionals apart from physicians (e.g. pharmacists, nurses) and even patients to report, introducing fees for reporting, coupling electronic

Table 1 Voluntary reporting of adverse drug reactions to the Cuban Pharmacovigilance System, 2000.

Number of reports received	28 450 (2 543/10^6 inhabitants)
Number of ADRs	39 777
Most frequently implicated organs/systems	
Body as a whole	8 258 (29.0% of reports received)
Gastrointestinal	5 899 (20.7% of reports received)
Skin and appendages	4 699 (16.5% of reports received)
Most frequent ADRs	
Rash	3 595 (9.0% of ADRs reported)
Vomiting	2 501 (6.3% of ARDs reported)
Nausea	2 297 (5.8% of ADRs reported)
Dizziness	2 049 (5.2% of ADRs reported)
Headache	1 982 (5.0% of ADRs reported)
Pruritus	1 466 (3.7% of ADRs reported)
Most frequent suspected groups of drugs (ATC Classification)	
Antibiotics for systemic use (J01)	5 965 (21.0% of reports received)
Anti-inflammatory and anti-rheumatic products, non steroidal anti-inflammatory drugs (M01A)	4 980 (17.5% of reports received)
Antihypertensives (C02)	2 558 (9.0% of reports received)
Most frequent suspected individual drugs	
Benzylpenicillin	3 021 (10.6% of reports received)
Nifedipine	2 442 (8.6% of reports received)
Indomethancin	2 110 (7.5% of reports received)
Number of reports describing severe ADRs	975 (3.4%)
Number of reports describing fatal ADRs	20 (0.1%)
Number of reports with previously undescribed ADR–drug associations	27 (0.1%)

reporting with electronic information systems and in software for electronic medical records, etc. Our approach consisted in integrating ADR reporting with training and continuous education of physicians. We feel that it is of special interest that this experience was developed in a less developed country, during a deep economic crisis, but with a universal and equitable health care system.

The efficiency of spontaneous reporting for detecting new, previously undescribed, ADRs depends both on the number and the quality of reports. Now that a high reporting rate has been achieved, the next step will be improving the relevance and quality of reporting, by specifically promoting reporting of suspicions of ADRs related with recently marketed drugs, and by encouraging reporting of severe and poorly known adverse events.

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